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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with chloromethane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to June, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-051. NTIS PB81-117624.

U.S. EPA. 1982. Errata for Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1983. Reportable Quantity Document for Methyl Chloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Methyl Chloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan).

This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Exposure to chloromethane vapor has been shown to increase the incidence of kidney tumors in male B6C3F1 mice (CIIT, 1981; NIOSH, 1984). No other studies regarding the carcinogenic potential of chloromethane by other routes were available. Because of the lack of data, U.S. EPA (1986a) calculated an oral q_1^* from the inhalation data. This value, 1.26×10^{-2} $(mg/kg/day)^{-1}$ is also presented in this document. An inhalation q_1^*, also calculated from the CIIT (1981) study, was determined to be 6.23×10^{-3} $(mg/kg/day)^{-1}$. Chloromethane has been classified by the U.S. EPA (1986a) as a Group C carcinogen.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EEG	Electroencephalogram
ppm	Parts per million
RfD	Reference dose
RfD_S	Subchronic reference dose
SCE	Sister-chromatid exchange
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposed level
TLV	Threshold limit value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and half-lives of chloromethane (CAS No. 74-87-3) are presented in Table 1-1.

The sources of atmospheric chloromethane are both natural and anthropogenic. Chloromethane is always present in the atmosphere at low concentrations, depending upon seasonal, diurnal and latitudinal variations (Khalil and Rasmussen, 1983; Singh et al., 1982). Reaction with HO radical is the most significant process for removal of chloromethane from the troposphere (Davis et al., 1982). Based on an estimated atmospheric half-life of ~1 year (Davis et al., 1976) and the lifetime for tropospheric to stratospheric transfer of 30 years (Dilling, 1982), ~3% of tropospheric chloromethane is expected to be transferred to the stratosphere where it may participate in the destruction of the ozone layer (Dilling, 1982). Volatilization from water is expected to be the dominant removal mechanism for aquatic chloromethane. Based on a recommended value for Henry's Law constant of 9.4×10^{-3} atm-m³/mol at 25°C (Mackay and Shui, 1981), the volatilization half-life from a depth of 1 m was calculated to be 3.8 hours by the method of Lyman et al. (1982). Based on the fate of chloromethane in water, it is speculated that volatilization is the most important removal mechanism from soil. Because of its low soil adsorption coefficient and relatively high water solubility, leaching of chloromethane from soil to groundwater may occur from dumpsites.

TABLE 1-1

Selected Chemical and Physical Properties of Chloromethane

Property	Value	Reference
Chemical class:	chlorinated aliphatic hydrocarbon	
Molecular weight:	50.49	
Vapor pressure:	3.6×10^3 mm Hg at 20°C	Mackay and Shui, 1981
Water solubility:	7.4×10^3 mg/ℓ at 20°C	Mackay and Shui, 1981
Log octanol/water partition coefficient:	0.91	Hansch and Leo, 1985
Bioconcentration factor:	3 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	25 (estimated)	Lyman et al., 1982
Half-lives in Air:	~1 year (estimated)	Davis et al., 1976
Water:	~4 hours (estimated) rapid flowing shallow	Lyman et al., 1982

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Pertinent data regarding absorption of chloromethane following oral administration could not be located in the available literature.

2.2. INHALATION

Putz-Anderson et al. (1981a) exposed men and women to chloromethane at 100 or 200 ppm (207 or 413 mg/m³) for 3 hours. Breath levels of exposed individuals reached equilibrium during the first hour. The average breath level for the eight 100 ppm-exposed individuals was 36±12 ppm (mean±S.D.). In the twenty-four 200 ppm-exposed subjects breath concentrations reached 63±23.6 ppm. Breath levels were highly correlated with blood levels ($r=0.85$ or 0.91, $p \leq 0.01$) that reached 7.7±6.3 ppm and 11.5±12.3 ppm in the low- and high-exposure groups, respectively. Rate of absorption or percent absorption were not estimated in this study.

Nolan et al. (1985) also exposed six male volunteers to 10 or 50 ppm (21 or 103 mg/m³) chloromethane for 6 hours. Blood and expired air concentrations of chloromethane reached equilibrium during the first hour. The expired air was found to contain 30-70% of the concentration of chloromethane in inhaled air. Absorption rates of 1.4-3.7 µg/minute/kg were calculated using a two-compartment pharmacokinetic model.

In a study by Morgan et al. (1970), volunteers inhaled a known concentration of ^{36}Cl-labeled chloromethane in a single breath. The amount of radioactivity expired in two breaths following breath-holding for 20 seconds was determined to be 22% of the inhaled dose. After 1 hour, 29% of the administered radioactivity was recovered in expired air. Therefore, 71-78% of the ^{36}Cl-chloromethane had been retained and potentially absorbed.

Landry et al. (1983) exposed groups of six male Fischer 344 rats to chloromethane vapor at 50 or 1000 ppm (103 or 2065 mg/m³) for 6 hours. Vapor uptake was measured at 1.5 and 2 hours of exposure. At both sampling times the uptake was 10 µg/minute/kg for the 50 ppm exposure level and 165 µg/minute/kg for the 1000 ppm exposure level. After 6 hours, the absorbed dose, calculated using a two-compartment model, was determined to be 3.8 mg/kg for the 50 ppm concentration and 67 mg/kg for the 1000 ppm concentration.

In an additional experiment, Landry et al. (1983) exposed male Fischer 344 rats for 6 hours and male beagle dogs for 3 hours to chloromethane vapor at 50 or 1000 ppm (103 or 2065 mg/m³). Chloromethane levels in the blood rose rapidly, reached a plateau and were proportional to exposure concentrations. Blood:gas concentration ratios were 1.5 and 1.8 for dogs exposed to 50 or 1000 ppm, respectively, and 1.8 and 1.9 for rats at 50 or 1000 ppm, respectively.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding subchronic effects of chloromethane following oral administration could not be located in the available literature.

3.1.2. Inhalation. In a study by Evtushenko (1966), groups of 10 rats and 4 rabbits were exposed to either 40 or 240 mg/m³ chloromethane vapor for 4 hours/day for up to 6 months. Decreased erythrocyte counts and depletion of lymphoid elements in the spleen and lymph were observed in rats at both exposure levels. Disturbed excretory function of the liver was observed in both rats and rabbits at 240 mg/m³. Discoloration of the optic disc and histological lesions of the retina and optic nerve were observed in rabbits at both exposure levels.

Mitchell et al. (1979) exposed groups of 10 male and 10 female Fischer 344 rats (6 weeks old) and 10 male and 10 female B6C3F1 mice (6 weeks old) to chloromethane vapor at 375, 750 or 1500 ppm (774, 1549 or 3098 mg/m³) for 6 hours/day, 5 days/week for 13 weeks Equal numbers of control rats and mice were observed for food consumption, body weight gain, clinical signs and mortality. At the end of the exposure period, blood and urine samples were taken for analysis, ophthalmic examinations were made and the rats and mice were sacrificed. Treatment-related effects observed in the high-dose groups were as follows: significantly increased SGPT activity in male mice, increased relative liver weights in male and female mice and female rats, hepatic infarctions in one male mouse and one female rat, and increased severity and incidence of cytoplasmic vacuolization of hepatocytes in male mice. Significantly reduced body weight gain in male and female rats in the 750 and 1500 ppm dose groups was the only other treatment-related effect observed.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding chronic effects of chloromethane following oral administration could not be located in the available literature.

3.2.2. Inhalation. Repko and Losley (1979) reviewed the toxic effects of chloromethane exposure in humans. Without providing dose information, they stated that long-term exposure to low levels of chloromethane tends to result in signs and symptoms confined almost exclusively to the CNS. The signs and symptoms observed include headaches, drowsiness, staggering, muscle weakness, slurred speech, confusion and impaired judgement.

Repko et al. (1976) conducted an epidemiology study that evaluated the behavioral and neurological effects of chloromethane in humans occupationally exposed to the compound for 1-311 months. Data from 122 exposed and 49 control workers (age 18-61) from several locations were analyzed. Ambient air concentrations were measured at 1.8-70 ppm (3.7-145 mg/m^3) with an average concentration of 33.57 ppm (69.32 mg/m^3). Breath levels of chloromethane, which ranged from 10.81-24.19 ppm (22.32-49.95 mg/m^3), were significantly correlated with ambient air levels ($p<0.005$). No significant differences were observed in the results of neurological examination or EEG activity. Behavioral tests showed that exposed workers had impaired performances on time-sharing tasks and increased magnitudes of finger tremors compared with controls. These changes correlated with chloromethane levels in ambient air and with urine pH, but no relationship between chloromethane in breath and performance was observed.

In a study by CIIT (1981), summarized by NIOSH (1984), groups of 120 male and 120 female Fischer 344 rats and 120 male and 120 female B6C3F1 mice were exposed to chloromethane vapor at 0, 50, 225 or 1000 ppm (0, 103, 465

or 2065 mg/m³) for 6 hours/day, 5 days/week for up to 24 months. Interim sacrifices were performed at 6, 12, 18 and 24 months of exposure. During the study, rats and mice were observed or evaluated for clinical signs, body weight gain and mortality. Just before sacrifice, ophthalmological examinations were made, hematological, clinical chemistry and urinalysis parameters were determined, and examinations for gross and histopathological lesions were made; neurofunction was also examined at 18-24 months. Male and female mice had increased mortality at 1000 ppm, while rats were not affected. Male mice at 1000 ppm showed a significant (p value not provided) decrease in growth rate through the first 18 months of the study. The growth rates of both male and female rats at 1000 ppm were significantly depressed (p value not provided) throughout the study. At 18, 21 and 22 months, neurofunctional impairment was observed in most male and female mice exposed to 1000 ppm. The impairment observed consisted of a positive clutch response at 18 months and a weakened extensor thrust/scratch response. At 6, 12 and 18 months, male mice at 1000 ppm showed significantly elevated SGPT levels that were associated with hepatocellular degeneration and necrosis. At 6 and 12 months, female mice at all exposure levels showed significant increases in SGPT. These increases were not observed at 18 or 24 months, and were not associated with liver lesions. Although there were a number of relative organ weight changes in both rats and mice, they were not consistently related to dose and were bi-directional.

The histopathological data (CIIT, 1981; NIOSH, 1984) showed a significant increase in the incidence of hepatic lesions (multifocal centrilobular hepatocellular necrosis, karyomegaly, cytomegaly and vacuolar degradation) in male and female mice at 1000 ppm as compared with controls ($p<0.0001$).

The kidneys of male mice exposed to 1000 ppm had significantly increased incidences of hyperplasia and karyomegaly of renal tubule epithelial cells compared with controls ($p<0.0001$). The kidney lesions were first observed at 12 months and became more severe as exposure continued. Male mice exposed to 1000 ppm also had significantly increased incidences of degeneration and atrophy of seminiferous tubules ($p=0.001$) and of the spleen ($p<0.0001$). The incidence of degeneration and atrophy of the cerebellar granular layer was also increased in 1000 ppm exposed male ($p<0.0001$) and female ($p<0.05$) mice compared with controls. An increase in the incidence of atrophy and degeneration of the seminiferous tubules of male rats exposed to 1000 ppm chloromethane was the only treatment-related histopathological lesion observed in rats.

A series of reports describe studies in which several species were exposed to chloromethane vapor 6 hours/day, 6 days/week for up to 64 weeks (Smith and von Oettingen, 1947a,b; Smith, 1947; Dunn and Smith, 1947). Exposure levels varied from as high as 4000 ppm (8260 mg/m^3) to a low of 300 ppm (620 mg/m^3). Deaths in all species occurred in 1-37 days at concentrations $\geq$1000 ppm (Smith and von Oettingen, 1947a). Rats were the only species that had no mortality in 211 days at 500 ppm (1033 mg/m^3). Toxic effects observed in dogs exposed to 500 ppm for up to 29 weeks were ataxic, and had severely impaired gait and tremors. At 500 ppm, monkeys became emaciated and prostrate before death at 16-17 weeks. Mice, rabbits and rats also experienced neuromuscular effects that often resulted in inability to use the hind legs. No toxic effects were observed in any species exposed to 300 ppm for 64 weeks. The histopathological changes in animals exposed to ~1000 ppm for 6 hours/day, 6 days/week until death, were variable degrees of necrosis of the convoluted tubules of the kidneys in

mice and rats, renal changes associated with hemoglobinuria in mice and occasionally in dogs, and a low to moderate amount of fatty metamorphosis of the liver and kidneys of mice, rats, rabbits and guinea pigs (Dunn and Smith, 1947).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding teratogenic and reproductive effects of chloromethane following oral administration could not be located in the available literature.

3.3.2. Inhalation. In a study by Wolkowski-Tyl et al. (1983a), groups of 74-77 female C57BL/6 mice that were mated to C3H male mice were exposed to chloromethane at 0, 250, 500 or 750 ppm (0, 516, 1033 or 1544 mg/m³) for 6 hours/day on gestation days 6-18. On gestation day 18, dams were killed. Dams exposed to 750 ppm had decreased body weights, tremors, convulsions and ataxia, and were hypersensitive to touch or sound. During the exposure period, six mice died and one was killed in extremis in the 750 ppm exposure group. The fetuses of both the 750 and 500 ppm groups had significantly ($p<0.05$) increased incidences of heart defects compared with controls. No effects were observed in the 250 ppm exposed group.

In a similar study by Wolkowski-Tyl et al. (1983b), groups of 25-33 pregnant Fischer 344 rats and C57BL/6 mice were exposed to chloromethane vapor at 0, 100, 500 or 1500 ppm (0, 207, 1033 or 3098 mg/m³) for 6 hours/day on gestation days 7-19 (rats) and gestation days 6-17 (mice). Rats and mice were sacrificed just before parturition and the numbers of live and resorbed fetuses were determined. Fetuses were then examined for abnormalities. In rats, maternal food consumption, body weight gain and terminal body weight were reduced at the high concentration. Fetal toxicity, manifested as statistically significantly reduced fetal body weights

(both sexes) and reduced fetal crown-rump length (females only), was also noted at the high concentration. No chloromethane-induced abnormalities were observed in rat fetuses. In mice, 1500 ppm chloromethane was severely toxic to dams after ≥4 days of exposure. Mice in the high-exposure group were killed in extremis on gestation days 10-14. Necropsy of the dams showed necrosis of neurons in the internal granular layer of the cerebellum. No maternal toxicity or fetotoxicity was observed in mice at the other exposure levels. Fetuses from the 500 ppm exposed dams showed a statistically significant ($p<0.05$) increase in the number of heart defects. At 100 ppm, no embryofetal toxicity or teratogenicity was observed in mice.

Chloromethane has been shown to cause reproductive effects in male rats. In a study by Morgan et al. (1982), groups of 10 male Fischer 344 rats were exposed to 0, 2000, 3500 or 5000 ppm (0, 4130, 7228 or 10,325 mg/m³) methyl chloride vapor, 6 hours/day for 5 days, to filtered air for 2 days, and then to chloromethane for 4 more days. After the last exposure, the rats were killed. Histological examination showed that all rats at the 2000 and 3500 ppm exposure levels had minimal testicular degeneration, while at 5000 ppm all rats had severe testicular degeneration. No testicular lesions were observed in control rats.

In a study by Chapin et al. (1984), adult male Fischer 344 rats were exposed to 3500 ppm (7228 mg/m³) chloromethane, 6 hours/day for 5 days, to filtered air for 3 days, and then to chloromethane, 6 hours/day for another 4 days. Control rats were exposed to filtered air. On postexposure days 5, 7, 9, 11, 13, 15, 19 and 70, groups of six or eight treated and two control rats were killed. On day 9, histopathological examination of the testis showed a delay in spermiation. On days 13-19, all treated rats showed varying degrees of disruption and disorganization of the seminiferous epithelium, which became more advanced as time from treatment increased.

Granulomas of the epididymis were observed on day 19. Most (70-90%) of the seminiferous tubules of rats sacrificed on day 70 postexposure were shrunken, and the remaining tubules showed varying degrees of spermatogenesis recovery. Chapin et al. (1984) also examined testosterone levels and found that serum testosterone concentrations showed a time-dependent decrease during the five consecutive chloromethane exposures (6 hours/day for 5 days).

In a dominant lethal assay, Working et al. (1985a) exposed groups of 40 male Fischer 344 rats to chloromethane vapor at 0, 1000 or 3000 ppm (0, 2065 or 6195 mg/m^3), 6 hours/day for 5 days. Each treated male was bred to one female weekly for 8 weeks. Female rats were killed 12-17 days after mating and data for dominant lethal effects were gathered. The results showed that reproductive performance and fertility of male rats exposed to 1000 ppm did not vary significantly from controls. At week 2, mating performance was depressed and at weeks 2 and 3 postexposure there were significantly fewer fertile males in the 3000 ppm treatment group. Though not significant, the percentage of fertile males in the 3000 ppm group remained less than controls throughout the breeding period. A significant increase in preimplantation loss at week 3 postexposure was the only dominant lethal parameter that differed from control values. The number of live and total implants from the 3000 ppm exposure group was decreased throughout the 8-week breeding period. Most of the decrease was a result of increased preimplantation loss. This loss was significant at weeks 2, 3, 4, 6 and 8 postexposure. Significantly increased postimplantation loss occurred only at 1 week postexposure. From these results, the authors concluded that the postimplantation losses may have been related to chloromethane-induced

dominant lethal mutations in sperm in the vas deferens and epididymis at the time of exposure, while the preimplantation losses may have been a result of cytotoxic effects as well as genotoxic effects.

In a second study by Working et al. (1985b), groups of 80 male rats were exposed to chloromethane vapor at 0, 1000 or 3000 ppm (0, 2065 or 2195 mg/m³), 6 hours/day for 5 days. Five rats from each group were killed every week for 8 weeks and at 16 weeks postexposure. Rats exposed to 3000 ppm had sperm granulomas in the caudal epididymis (15/39), which were first observed 16 days after the start of chloromethane exposure. Testes of the 1000 ppm exposed group exhibited normal morphology. In the 3000 ppm exposed group, testes showed evidence of disruption of spermatogenesis. Signs of toxicity were still evident 8 weeks postexposure, but at 16 weeks post-exposure most of the seminiferous tubules (50-90%) appeared normal. Sperm counts from the 3000 ppm exposure group were significantly decreased by 1 week postexposure, and there was an increased number of sperm with abnormal head morphology. By the third week following exposure, sperm motility was depressed and there was an increase in the frequency of headless sperm. By week 16 (except for sperm count which remained low), other parameters were near normal. No effects on sperm were noted in the rats exposed to 1000 ppm.

Hamm et al. (1985) conducted a 2-generation reproductive study in Fischer rats exposed to chloromethane vapor. Groups of 40 male and 80 female rats were exposed to chloromethane vapor at 0, 150, 475 or 1500 ppm (0, 310, 981, 3098 mg/m³), 6 hours/day, 5 days/week for 10 weeks. After 10 weeks, each male was mated to two exposed females and the exposure was changed to 6 hours/day, 7 days/week. After a 2-week mating period, males were removed from exposure and mated for an additional 2 weeks with

unexposed females. Females in treated groups were not exposed from gestation day 18 to postnatal day 4. For 10 weeks, members of the F_1 generation were exposed to the same chloromethane concentration as their parents (0, 150 and 475 ppm) and were then mated.

Results showed a significant decrease in body weight gains in the 1500 ppm F_0 males and females after 2 weeks, and in the 475 ppm males and females after 57 days. No litters were produced from males exposed to 1500 ppm with either exposed or unexposed females. Exposed and unexposed females mated to 475 ppm males produced significantly fewer litters than controls. No effects on litter size, sex ratio, pup viability, pup survival or pup growth were noted in the 475 and 100 ppm groups. Results of the F_1 breedings were not significantly different from controls, either biologically or statistically, although a trend toward decreased fertility was noted at 475 ppm.

3.4. TOXICANT INTERACTIONS

Putz-Anderson et al. (1981a) studied the effects of chloromethane and diazepam on CNS performance in humans. Volunteers were exposed to chloromethane at 200 ppm (413 mg/m³) for 3 hours, were given 10 mg diazepam, or received both treatments. Performance was then measured in a visual-vigilance task, a dual task and a time discrimination task. Diazepam caused a 10% average decrease in overall performance; chloromethane caused a decrease of 4%. Combined, the two treatments caused an average decline of 13.5% indicating that the effects of methyl chloride and diazepam are additive.

Putz-Anderson et al. (1981b) also studied the effects of chloromethane with caffeine and ethanol on humans. Male and female volunteers were exposed to methyl chloride at 0 or 200 ppm (413 mg/m³) for 3 hours along

with a drug treatment of ethanol (0.8 mL/kg absolute ethanol), caffeine (3 mg/kg) or a placebo. Performance tests used were the same as in the previous study. The results showed that chloromethane exposure at 200 ppm did not significantly change the effects of ethanol or caffeine.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the potential carcinogenicity of chloromethane in humans by oral or inhalation exposure could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Pertinent data regarding the potential carcinogenicity of chloromethane in animals following oral exposure could not be located in the available literature.

4.2.2. Inhalation. A 2-year inhalation study in mice and rats was conducted (CIIT, 1981), in which groups of 120 male and 120 female B6C3F1 mice and equal numbers of male and female Fischer rats were exposed to chloromethane vapor at 0, 50, 225 or 1000 ppm (0, 103, 465 or 2065 mg/m^3) for 6 hours/day, 5 days/week. At 6, 12, 18 and 24 months, 5-20 rats and mice/sex/group were killed. High mortality was observed in mice in the 1000 ppm group so that only two survived until 21 months, at which time they were sacrificed. Comprehensive histological examinations of all control and 1000 ppm mice and rats were made. Histological examination of the 50 and 225 ppm groups were limited to testes, epididymis, kidneys, liver and lungs for rats and liver, kidneys, spleen and brain for mice.

Although survival appeared to be reduced in 1000 ppm mice of both sexes, a statistically significant increase in mortality occurred only in females. A significant increase in the incidence of renal tumors was observed in male mice. Table 4-1 shows the numbers of male mice killed or dying, and the incidence of renal tumors in each month from the 12th month (when the first kidney tumor was found). Tumor types found were renal cortical adenomas, renal cortical adenocarcinomas, papillary cystadenomas, tubular cystadenomas

TABLE 4-1

Numbers of Male Mice Sacrificed or Dying and Kidney Tumor Prevalence in Months 13-24[a,b]

Month	Control	50 ppm	225 ppm	1000 ppm
13	12	10	10	11 (1A)
14	1	0	0	3
15	3	0	0	4
16	0	0	0	2
17	2	0	0	3 (1A, 1C)
18	1	0	0	3
19	6	5	5	11 (3A)
20	3	4	2	17 (4A)
21	6	5	1	24 (4A, 4C)
22	3	0	3	3
23	4	1	0	0
24				
TOTAL	26/67	36/61	36/57 (2A)	1/82

[a]Source: CIIT, 1981; NIOSH, 1984

[b]Parentheses indicate numbers of mice with kidney tumors, classified as adenomas (A) or carcinomas (C)

and papillary cystadenocarcinomas. The incidences of kidney tumors, as indicated on Table 4-1, were 0/67 controls, 0/61 in the 50 ppm group, 2/57 in the 225 ppm group and 18/82 in the 1000 ppm group. The above incidences do not account for kidney tumors that may have developed if the mice that were sacrificed at interim kills or died during the experiment had lived to 24 months. To correct for intercurrent mortality, the method described by Peto et al. (1980) was applied. The "corrected" incidences of renal tumors in male mice are presented in Table 4-2. No evidence of treatment-related oncogenicity was observed in female mice or male or female rats.

4.3. OTHER RELEVANT DATA

Chloromethane has been shown to be positive for reverse mutation in Salmonella typhimurium strains TA1535 (Andrews et al., 1976) and TA100 (Simmon et al., 1977; Simmon, 1978, 1981) both in the presence and absence of S-9 metabolic activation. Chloromethane has also been found to be positive for forward mutations in S. typhimurium TA677 and human lymphoblasts and for SCE in human lymphoblasts without metabolic activation (Fostel et al., 1985). In a dominant lethal study, Working et al. (1985a,b) found that chloromethane induced dominant lethal mutations in mature sperm of Fischer 344 rats exposed to 3000 ppm (6195 mg/m^3), 6 hours/day for 5 days.

4.4. WEIGHT OF EVIDENCE

The increased incidence of kidney tumors in male mice, as supported by the positive mutagenicity data, constitutes limited animal evidence for carcinogenicity and as such means that chloromethane would fall within a U.S. EPA Group C classification, "possible" human carcinogen (U.S. EPA, 1986b).

TABLE 4-2

Carcinogenic Potency of Chloromethane (99.99% pure) in Male B6C3F1 Mice Exposed by Inhalation 6 Hours/Day, 5 Days/Week[a]

Dose ppm (ug/m³)	Duration of Treatment	Duration of Study (months)	Target Organ	Tumor Type	Tumor Incidence[b]
0 (0)	up to 24 months	24	NA	NA	0/67
50 (103)	up to 24 months	24	NA	NA	0/67
225 (465)	up to 24 months	24	kidney	cortical adenoma, adenocarcinoma papillary cystadenomas, tubular and papillary cystadenocarcinoma	2/57
1000 (2065)	most dead by 21 months	24	kidney	cortical adenoma, adenocarcinoma papillary cystadenomas, tubular and papillary cystadenocarcinoma	22/87[c]

[a]Source: CIIT, 1981

[b]Tumor incidences adjusted for intercurrent mortality by the method of Peto et al. (1980)

[c]Statistically different from control ($p=4.5\times10^{-7}$) by Fishers Exact test performed at SRC.

NA = Not applicable

5. REGULATORY STANDARDS AND CRITERIA

The ambient water quality criterion for chloromethane is 19 mg/ℓ (U.S. EPA, 1982). This level is based on an RfD of 0.54 mg/kg/day, which was calculated from a TLV of 50 ppm (105 mg/m³) (U.S. EPA, 1980a). The ACGIH (1985, 1986) TLV of 50 ppm is based on human exposure data that show no irreversible systemic effects at 100-200 ppm, and the observations of Repko et al. (1976) that neurotoxic effects may occur at lower exposures. The STEL adopted by ACGIH (1985) is 100 ppm (205 mg/m³) for 15 minutes. A permissible exposure limit for chloromethane is not listed by OSHA (1985).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Since chloromethane has been shown to be a carcinogen in male mice, an RfD_S will not be determined.

6.2. REFERENCE DOSE (RfD)

Since chloromethane has been shown to be a carcinogen in male mice, an RfD will not be determined.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Pertinent data regarding the carcinogenic potential of chloromethane following oral administration could not be located in the available literature. Because of the lack of oral data, the U.S. EPA (1986a) calculated an oral q_1^* from the inhalation data (see Section 6.3.2.) by applying an absorption factor of 0.5. The resultant value of 1.26×10^{-2} $(mg/kg/day)^{-1}$ was obtained.

6.3.2. Inhalation. An inhalation q_1^* was calculated using the multistage model of Howe and Crump (1982) from the CIIT (1981) study that showed an increase in kidney tumors from male mice. A statistically significant increase in the incidence of benign and malignant kidney tumors was observed in the high-dose male mice compared with controls (see Section 4.2.2.). Because the CIIT (1981) study used interim kills, the incidences of kidney tumors were corrected for intercurrent mortality by the method of Peto et al. (1980). The q_1^* was calculated using the multistage model developed by Howe and Crump (1982). The data used to calculate the inhalation q_1^* are presented in Table 6-1. The unadjusted q_1^* is 4.77×10^{-4} $(mg/kg/day)^{-1}$ while the human q_1^* is 6.32×10^{-3} $(mg/kg/day)^{-1}$.

TABLE 6-1

Derivation of a q_1^* for Inhalation Exposure

Compound: Chloromethane

Reference: NIOSH, 1984; CIIT, 1981

Species/strain/sex: mouse, B6C3F1, male

Route/vehicle: inhalation, air

le = 24 months

LE = 24 months

L = 24 months

bw = 0.03 kg (measured)

Tumor type and site: kidney adenoma or carcinoma

Experimental Doses or Exposues (mg/m^3, 6 hours/day, 5 days/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	0	0/67
103	24	0/61
656	152	2/57
2065	480	22/82

Unadjusted q_1^* from study = 4.7673305×10^{-4} $(mg/kg/day)^{-1}$

Human q_1^* = 6.3238234×10^{-3} $(mg/kg/day)^{-1}$

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APPENDIX

Summary Table for Chloromethane

Route	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Adjusted q_1^* or Unit Risk	Reference
Inhalation	mice	0, 50, 225 or 1000 ppm (0, 103, 656 or 2065 mg/m³, 6 hours/day, 5 days/week for 24 months; 0, 24, 152, 240 mg/kg/day	kidney tumors adenoma or carcinoma	6.32×10^{-3} $(mg/kg/day)^{-1}$	CIIT, 1981; NIOSH, 1984
Oral	see Section 6.3.1.				